QUALITY BY DESIGN BASED FORMULATION AND CHARACTERIZATION OF POORLY WATER SOLUBLE DRUG VIA ADVANCED SOLUBILITY ENHANCEMENT TECHNIQUES

SYNOPSIS

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INTRODUCTION

Efficient drug absorption and reproducible bioavailability and/or pharmacokinetic profile in humans are recognized today as one of the major challenges in oral delivery of new drug substances (Anand et al., 2011). Therapeutic efficiency of a drug is dependent on the bioavailability and eventually upon the solubility and absorption of drug molecules (Kansara et al., 2015). The solubility is an important parameter to achieve the required concentration of drug in the systemic circulation and hence to attain the biological activity of the drug in the body. As a matter of fact, more than one-third of the drugs listed in the U.S. Pharmacopoeia fall into the poorly water-soluble or water-insoluble categories. Today, about 40 per cent of new drug molecules discovered by the pharmaceutical industry are poorly soluble or lipophilic compounds (Humberstone & Charman, 1997). It was reported a couple of decades ago that more than 41% of the failures in new drug development have been attributed to poor biopharmaceutical properties, including water insolubility (Maheshwari et al., 2015; Nayaz et al., 2013).

The solubility issues can affect the oral delivery of the new drugs and also the delivery of many existing drugs. The drugs with poor solubility exhibit many in vitro formulation related difficulties, such as restricted choices of delivery of drug and highly complex dissolution testing with inadequate correlation to the in vivo absorption (Vasconcelos et al., 2007). These types of issues with in vivo and in vitro characteristics and the problems in attaining expected and reproducible in vivo/in vitro correlations (IVIVC) are often due to solubility issues with many newly synthesized compounds (Sultana et al., 2015). Hence, it is essential to improve the solubility of such drugs by applying different solubility enhancement techniques.

The Biopharmaceutical Classification System (BCS): The BCS is a scientific approach based on the aqueous solubility and intestinal permeability characteristics of the drug substance or substances. The BCS categorizes drug substances into one of four BCS classes as follows:

- Class I: high solubility, high permeability
- Class II: low solubility, high permeability
- Class III: high solubility, low permeability
- Class IV: low solubility, low permeability

Solubility

A drug substance is classified as highly soluble if the highest single therapeutic dose is completely soluble in 250 milliliter (mL) or less of aqueous media over the pH range of 1.2–6.8 at 37±1°C.

Permeability

The assessment of permeability should preferentially be based on the extent of absorption derived from human pharmacokinetic studies, e.g., absolute bioavailability or mass balance. High permeability can be concluded when the absolute bioavailability is ≥85%. High permeability can also be concluded if ≥85% of the administered dose is recovered in urine as unchanged (parent drug), or as the sum of parent drug, Phase 1 oxidative and Phase 2 conjugative metabolites. (M9 Biopharmaceutics Classification System- Based Biowaivers Guidance for Industry, 2021)

Solubility Enhancement Techniques: Conventional and Advanced Approach

Numerous methodologies have been suggested and practically applied to improve the marketability of drug candidates whose development is limited by drug solubility, dissolution rate and absorbability. These include the use of particle size manipulation via micronization and nanonization, use of complexing agents such as cyclodextrins, the preparation of high energy drug states related to polymorphic or amorphic transformations use of co-solvents, micellar solutions and lipid based systems for lipophilic drugs (Hirayama et al., 1997). The strategies that can be used for this purpose can be broadly classified into: formulation based approach and structure based approach. The former involves inclusion of various solubility enhancers such as hydrophilic polymers, cyclodextrins, surfactants, oils and liposomes which produce an apparent increase in solubility. The second approach involves modification either in the physical structure or chemical structure. The various techniques used for solubility enhancement are further classified as follows:

Physical modifications

- Particle size reduction
    - Micronization
    - Sonocrystallization
- Crystal engineering
    - Modification of crystal habit

- Polymorphs
- Pseudopolymorphs

❖ Drug dispersion in carriers

- Eutectic mixtures
- Solid dispersions
- Solid solutions

❖ Complexation

- Use of complexing agents like cyclodextrins

❖ Lipid-based systems

- Microemulsions
- Self-emulsifying drug delivery systems

Chemical Modifications

- Formation of salts and prodrugs
- Cosolvency
- Co-crystallization
- Hydrotrophy
- Solubilizing agents
- Liquisolid technology

❖ **Nanotechnology Based Approaches**

- Nanosponges
- Nanocrystals
- Nanosuspensions

LITERATURE REVIEW

Amorphous solid dispersions (ASDs) Drug solubility and dissolution rate of poorly water-soluble drugs can be successfully improved by formulating them as ASDs (Brough & Williams, 2013; Vasconcelos et al., 2007; Leuner & Dressman, 2000; Serajuddin et al., 1999; Navnit Shah et al., 2014; Van den Mooter, 2012). **ASD is a solid dispersion in which the active ingredient is dispersed within an excipient matrix in a substantially amorphous form** (Chiou & Riegelman, 1971). The amorphous state of the drug in ASDs is critical for increasing their solubility (Hancock & Zografi, 1997). With the drug in an amorphous form, no energy is required to break the drug crystal lattice. For this reason, relative to the crystalline form, the amorphous form of many poorly water-soluble drugs

can achieve substantially higher apparent solubility and markedly faster dissolution (Vaka et al., 2014). ASDs are also known to result in higher membrane flux due to a higher supersaturation (Miller et al. 2012) and thus, improve bioavailability (Shah N et al., 2013). ASDs also have a higher wettability due to the presence of hydrophilic polymers (Vasconcelos et al., 2007).

Based on formulation composition, solid dispersions are classified as **first, second, or third generation** (Tekade & Yadav, 2020). Solid dispersions prepared using crystalline carriers are the first generation. Their drug release rate is generally slower than the other two generations of solid dispersions (Kim et al., 2011). ASDs, which consist of an amorphous drug in combination with an amorphous polymer, constitute the second generation (Vasconcelos et al., 2007; Bindhani & Mohapatra, 2018). ASD formulations could also contain additional excipients, such as additional polymer and/or surfactants to further enhance drug release and stability (Vo et al., 2013). Such ASDs are known as the third generation.

Due to their solubility and dissolution advantages, ASD formulations have drawn increasing interest over the last decade, in both academia and industry (Bindhani & Mohapatra, 2018; Baghel et al., 2016; Ma X & Williams III, 2019; Pandi et al., 2020, Jermain et al., 2018; Singh et al., 2017). Table 1 summarizes the US Food and Drug Administration (FDA)-approved pharmaceutical products based on ASDs (Jermain et al. 2018; Vasconcelos et al., 2016). There has been an increase in the number of ASDs under development and reaching the market over the last decade (Vasconcelos et al., 2007; Vo et al., 2013). Currently, there are numerous methods available for ASD preparation, each of which has its advantages as well as limitations.

Table 1 Examples of FDA-approved products that are based on amorphous solid dispersions.

Trade name	**Chemical name**	**Manufacturing technique**	**Company**	**Year of Approval**
Cesamet®	Nabilone	Solvent evaporation	Meda Pharmaceuticals	1985
Isoptin® SR	Verapamil	Melt extrusion	Ranbaxy Laboratories	1987
Sporanox®	Itraconazole	Fluid bed bead layering	Janssen	1992

Trade name	Chemical name	Manufacturing technique	Company	Year of Approval
Prograf®	Tacrolimus	Spray drying	Astellas Pharma	1994
NuvaRing®	Etonogestrel/Ethinyl Estradiol	Melt extrusion	Merck	2001
Kaletra®	Lopinavir/Ritonavir	Melt extrusion	AbbVie	2007
Intelence®	Etravirine	Spray drying	Janssen	2008
Modigraf®	Tacrolimus	Spray drying	Astellas Pharma	2009
Zortress®	Everolimus	Spray drying	Novartis	2010
Norvir® Tablet	Ritonavir	Melt extrusion	AbbVie	2010
Onmel®	Itraconazole	Melt extrusion	Merz Pharma	2010
Incivek®	Telaprevir	Spray drying	Vertex	2011
Zelboraf®	Vemurafenib	Solvent/anti- solvent precipitation	Roche	2011
Kalydeco®	Ivacaftor	Spray drying	Vertex	2012
Noxafil®	Posaconazole	Melt extrusion	Merck	2013
Astagraf XL®	Tacrolimus	Wet granulation	Astellas Pharma	2013
Belsomra®	Suvorexant	Melt extrusion	Merck	2014
Harvoni®	Ledipasvir/Sofosbuvir	Spray drying	Gilead Sciences	2014
Viekira XR™	Dasabuvir/Ombitasvir/Paritaprevir/ Ritonavir	Melt extrusion	AbbVie	2014
Epclusa®	Sofosbuvir/Velpatasvir	Spray drying	Gilead Sciences	2016
Orkambi®	Lumacaftor/Ivacaftor	Spray drying	Vertex	2016
Venclexta®	Venetoclax	Melt extrusion	AbbVie	2016
Zepatier®	Elbasvir/Grazoprevir	Spray drying	Merck	2016

Trade name	**Chemical name**	**Manufacturing technique**	**Company**	**Year of Approval**
Stivarga®	Regorafenib	-	Bayer	2017
Mavyret™	Glecaprevir/Pibrentasvir	Melt extrusion	AbbVie	2017
Trade name	Chemical name	Manufacturing technique	Company	Year of Approval
Lynparza®	Olaparib	Melt extrusion	AstraZeneca	2018
Orilissa®	Elagolix	Wet granulation	AbbVie	2018
Erleada®	Apalutamide	Spray drying	Janssen	2018
Trikafta®	Elexacaftor (Crystalline)/Ivacaftor/Tezacaftor	Spray drying	Vertex	2019
Symdeko®	Tezacaftor/Ivacaftor and Ivacaftor	Spray drying	Vertex	2019
Braftovi®	Encorafenib	Melt extrusion	Pfizer	2020
Oriahnn™	Elagolix/estradiol/norethindrone acetate	Melt extrusion	AbbVie	2020

Table 2 Commonly used polymers for ASD preparation.

Polymer	**T_g (°C)**	**Solubility in solvents**
Hydroxypropyl methylcellulose	175–185	Water, ethanol:dichloromethane (1:1, 2:1), methyl acetate:methanol (1:1)
Hydroxypropyl methylcellulose acetate succinate	100–110	Caustic water, acetone, methanol, dichloromethane, chloroform
Hydroxypropyl methylcellulose phthalate	133–137	Water, acetone, ethyl acetate, methyl ethyl ketone, ethanol:dichloromethane (1:1) methanol, dichloromethane, tetrahydrofuran

Polymer	T_g (°C)	Solubility in solvents
Polyvinylpyrrolidone	175–180	Water, acetone, ethanol, methanol, ethyl acetate, methyl ethyl ketone, dichloromethane, tetrahydrofuran
Polyvinylpyrrolidone/vinyl acetate	70–110	Water, acetone, ethanol, methanol, ethyl acetate, methyl ethyl ketone, dichloromethane, tetrahydrofuran
Polymethacrylates derivatives (Eudragit®-L100, S100)	>150	Water (only L100), acetone, ethanol, methanol, ethanol:dichloromethane (1:1)
Cellulose acetate phthalate	160–170	Acetone, ethyl acetate, methyl ethyl ketone
Soluplus®	72	water, acetone, ethanol, methanol, dichloromethane

Table 3 General factors impacting the stability of amorphous solid dispersions

Factor (Increase)	Stability	Cause	Ref.
Glass transition temperature (Tg)	Increases	Anti-plasticization effect by polymers	Li et al., 2015
Molecular mobility	Decreases	Molecular mobility is directly responsible for drug recrystallization	Nunes et al., 2014
Configurational entropy	Increases	Low configurational entropy will favor Crystallization	Graeser et al., 2009
Configurational enthalpy	Decreases	The greater thermodynamic driving force for crystallization causes an increased rate of nucleation	Marsac et al., 2006
Drug chemical potential	Decreases	Systems with lower drug chemical potential are generally more stable	Guo et al., 2013

Factor (Increase)	Stability	Cause	Ref.
Humidity, mechanical stress, and temperature	Decreases	These factors can significantly increase molecular mobility and may plasticize the material	Sarode et al., 2013
Polymer concentration	Increases	Kinetic stabilization	Van den Mooter et al., 2012
Surfactant concentration	Decreases	Enhance nucleation, accelerate solution mediated crystallization	Canselier et al., 1994

Review of work done on Solid dispersion

Soluplus® is an amorphous, tri-block, graft co-polymer with polyvinyl caprolactam, polyvinyl acetate, and polyethylene glycol (PCL: PVAc: PEG6000) in the ratio 57:30:13. PEG 6000 (BASF) is a waxy material with melting point of about 60 °C. **Altamimi & Neau, 2017** evaluated the physicochemical and in vitro characteristics of solid dispersions using BCS II model drugs (Nifedipine (NIF) and sulfamethoxazole (SMX)) with Soluplus® and one of its component homopolymers, PEG 6000. Solid dispersions were successfully prepared using lyophilization and spray drying techniques. Each polymer enhanced the drug dissolution rate; NIF dissolution rate was improved to a greater extent. Due to hydrophilic nature of PEG 6000, the dispersions prepared with PEG 6000 gave a faster dissolution rate. Differential Scanning Colorimetric analysis proved the absence of crystalline material in the dispersions.

Alves et al., 2014, prepared a solid dispersion of efavirenz, a drug with low solubility, in Polyvinylpyrrolidine K-30 by using conventional solvent evaporation and kneading methods. Solvent evaporation technique for the preparation of solid dispersion proved unsatisfactory, resulting in a decreased dissolution rate, despite the amorphous state of the samples, while the solid dispersion by kneading method 4:1 (EFV:polymer) and physical mixtures (PM) had a higher rate of dissolution. This system has also proved advantageous in terms of stability, after DSC evaluation, because there was insignificant degradation of the drug after being subjected to adverse storage conditions.

Chen et al., 2010, worked on the improvement of the oral bioavailability of Ginkgo biloba extract (GBE) through preparing G. biloba extract phospholipid complexes (GBP) and G. biloba extract solid dispersions (GBS). Authors prepared the GBP and GBS and studied their physicochemical properties by powder X-ray diffraction (XRD), differential scanning calorimetry (DSC), and dissolution. Finally, the pharmacokinetic characteristics and bioavailability of quercetin, kaempferol and isorhamnetin, was checked in rats after oral administration of GBP and GBS comparing with GBE. The results showed that the bioavailability in rats was increased remarkably.

KinetiSol® Dispersing, a rapid high energy thermal manufacturing process, was investigated by **DiNunzio et al., 2010**, for the ability to produce amorphous solid dispersions without the aid of a plasticizer. The itraconazole was used as a model API and for solid dispersion model carriers, Eudragit® L100-55 and Carbomer 974P were used. Triethyl citrate (TEC) was used a model plasticizer. Solid dispersions prepared by KinetiSol® Dispersing and hot melt extrusion were evaluated for supersaturated in vitro dissolution behavior under pH change conditions, solid state properties and accelerated stability performance. A significantly higher dissolution rate of plasticized material was observed in supersaturated in vitro dissolution testing, which was attributed to the pore forming behavior of TEC during the acidic phase of testing. X-ray diffraction testing revealed that under accelerated stability conditions for 6-month, partial recrystallization of plasticized compositions was happening, while plasticizer free materials remained amorphous throughout the testing period. These results confirmed that KinetiSol® Dispersing could be used for the production of amorphous solid dispersions without the use of a plasticizer.

The drugs with poor water solubility tend to have low bioavailability, which can be improved by preparing the solid dispersions of the drug. **Frizon et al., 2013** prepared the solid dispersions of a BCS class II drug, loratadine, by rotary evaporation and spray-drying solvent evaporation techniques using polyvinylpyrrolidone K-30 as hydrophilic carrier. Results revealed the increase in solubility of the drug, especially in acid medium, and an enhancement in dissolution profiles. Both methods, used for the preparation of solid dispersion, proved to be equally satisfactory, when compared to physical mixtures. The results were attributed to reduction in particle size of the drug with increased surface area, increase in wettability due to intimate contact of the drug with the hydrophilic matrix and the conversion of the crystalline to the amorphous state.

Ganapuram et al., 2013, prepared and evaluated Irbesartan loaded surface solid dispersions (SSD) for enhancing the solubility and bioavailability of poor soluble drug. Five different super disintegrants were used for the preparation of SSD by co-evaporation method, in three different drug-carrier ratios. The P-XRD studies of prepared formulations showed decrease in crystallinity of drug formulations when compared to the pure state of the drug. The SEM images exhibited irregular matrices due to the porous nature of the carrier with the fine particles of the drug embedded in it. The in vitro dissolution studies of SSD of crospovidone with drug to carrier ratio of 1:10 showed highest dissolution rate with the dissolution efficiency of 98.18% (10 min) in comparison to the other formulations.

Khan et al., 2015, enhanced the dissolution rate of Hydrochlorothiazide (Class II Drug) by using two techniques namely, solid dispersion and liqui-solid techniques (Vo et al., 2013). Both the techniques enhanced the dissolution rate of drug to a greater extent when compared with conventional tablet in terms of dissolution efficiency, similarity factor and dissimilarity factor. But liqui-solid technique was found to be more effective in enhancing rate and extent of drug release.

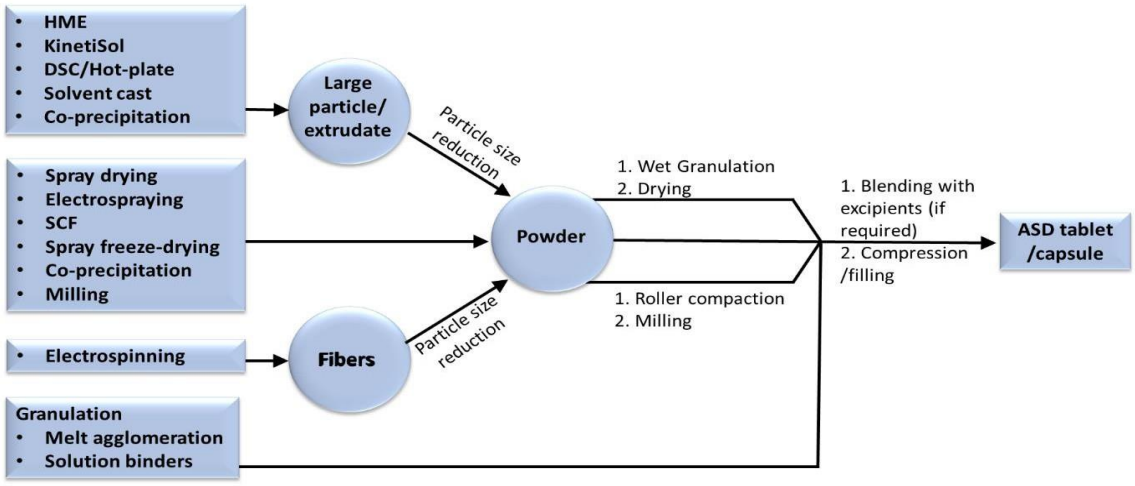
Kogermann et al., 2013, checked the influence of different polymers, with varying physicochemical properties, on the stability and dissolution of co-milled amorphous solid dispersions (ASDs) of piroxicam (PRX) (Baghel et al., 2016). The results indicated the significant improvement in the stability of amorphous PRX (aPRX) in ASDs by the polymers. Raman spectroscopy revealed that solvent mediated solid state changes occurred in biorelevant medium, hence the dissolution behavior of ASDs of PRX and the respective polymer during conventional large volume (900 ml) and a small volume (20 ml) dissolution testing was evaluated. The results of these studies showed that the solubility of piroxicam from ASD is affected by the molecular weight of the polymer.

Lu et al., 2014, prepared the solid dispersion of simvastatin (SV) and polyvinylpyrrolidone (PVP) to understand the relationship of wettability with dissolution of drug. To elucidate this relationship, the dissolution, contact angle and water absorption rate of these solid dispersions were measured. The results showed the decrease in contact angle with increase in PVP concentration which produced the increase in dissolution efficiency of the solid dispersion.

Mohammadi et al., 2014, did the in vitro and in vivo evaluation of clarithromycin–urea solid dispersions, prepared by solvent evaporation, electro-spraying and freeze drying methods. The physicochemical properties of the prepared solid dispersions were also evaluated. Scanning electron microscopic images proved that the microsize crystals were obtained by freeze drying method. All the solid dispersions showed faster drug release in comparison with pure drug, which was supported by the improved bioavailability by oral pharmacokinetic studies performed in the rabbits.

Manufacturing methods for preparing amorphous solid dispersions:

The schematic of downstream processing routes to prepare ASD solid dosage forms as shown in below figure 1. Based on lab resources and feasibility, following some techniques explained in details in below sections.



A. Solvent evaporation-based methods

The solvent evaporation processes for preparing ASDs essentially involve drug–polymer dissolution in organic solvent systems and their subsequent evaporation. Aqueous solvents can also be used in conjunction with organic systems to enhance polymer solubility, and/or reduce the extent of organic solvent usage. Amorphous drug–polymer dispersion is generated by rapidly evaporating the solvent from the drug–polymer solution. Because organic solvent evaporation is an important consideration when developing an ASD using a solvent evaporation process is the choice of a solvent system. The most challenging aspect of this method is obtaining a solvent system that can solubilize the drug–polymer system and be compatible with the formulation (Paudel et al., 2013) and has a low residue in the product. Poor or partial solubility of the constituents may lead to longer processing

times and non-homogenous ASDs. In order to obtain the desired solvent parameters, often a combination of solvents is used. In such cases, azeotrope forming solvents such as water with ethanol (95.5%, w/w) or isopropanol (87.7%, w/w) are preferred. This is because binary solvents with different evaporation rates can cause a variable degree of supersaturation that can result in rapid precipitation of selective components at some point in the evaporation process. Such an event generates a strong potential for phase separation (Li et al. 2020). Similarly, significant differences in the solubility of components can result in a faster rate of drying and selective precipitation of the component with lower solubility on the droplet surface (Bercea M et al., 2009). This in turn could further affect ASD stability. The solvent should not affect the physical or chemical stability of the formulation constituents during the manufacturing process before being evaporated from the system.

A1. Spray drying

Spray drying is one of the widely used processes for manufacturing ASDs (Ogawa et al., 2018) because it is a continuous and commercially scalable drying process (Mujumdar, 2015). The schematic set-up of the process is presented in Figure 2. The spray drying process constitutes several steps. First, the feed solution/suspension containing the drug and the polymer (and possibly other additives) is pumped into the drying chamber through a spray-nozzle. The different types of commonly used nozzles are shown in Fig. 2 (b, c, d). The two-fluid nozzle has been the most commonly used nozzle for preparing spray-dried ASDs, particularly on a laboratory-scale (Orzechowski Z, 1993) The energy required to atomize the liquid is primarily provided by a gas. Liquid fed into the nozzle under low pressure can be mixed either internally or externally with the gas (Lefebvre & Mcdonell, 2017). Another widely used nozzle in the pharmaceutical industry is the pressurized nozzle (Beyerinck et al., 2004; Beyerinck et al., 2010) which solely uses the feed liquid pressure for atomization. The potential energy of liquid is converted into kinetic energy within the

pressure-swirl nozzle.

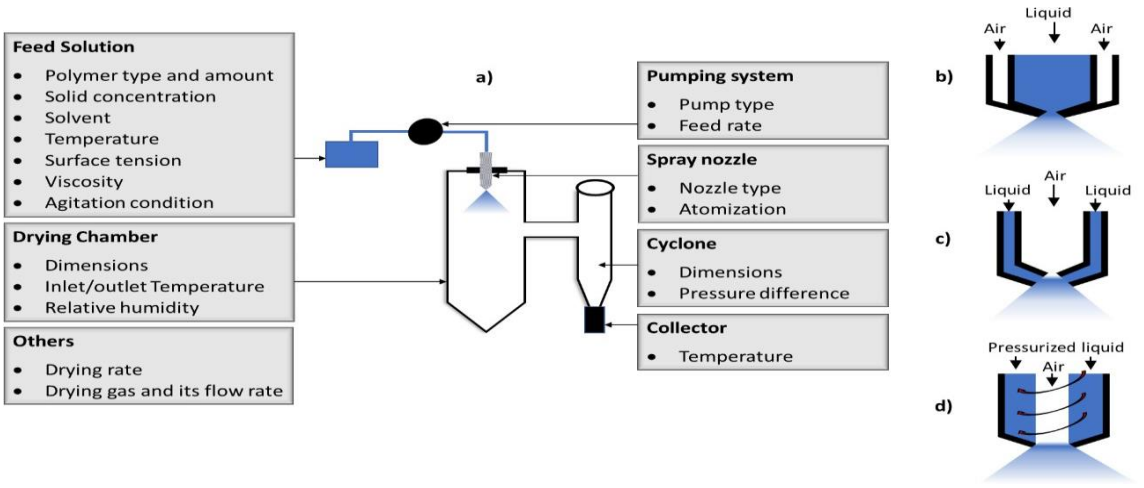


Figure 2: A schematic of (a) spray dryer set-up and the manufacturing variables affecting product properties and performance; (b) external mixing two-fluid nozzle; (c) internal mixing two-fluid nozzle; (d) pressure-swirl nozzle

A2. Fluidized bed technology

Fluid bed technology is used for various pharmaceutical unit operations including granulation (fluidized bed granulator), coating (fluidized bed coater), drying (fluidized bed dryer), and cooling (Tamrakar & Ramachandran 2019; Wentzlaff et al., 2019; Rajabi-Siahboomi, 2018). Along similar lines, fluidized bed coaters and granulators are also used to manufacture ASDs (Kwon et al., 2019). For ASD preparation, the drug-polymer solutions are sprayed onto inert excipient cores, with the solvent evaporation and ASDs layering occurring simultaneously. The organic solvent can be recovered and recycled (Nandi et al., 2015). This method has been used to formulate both controlled- and immediate-release solid dispersions (Benten et al., 1995; Ho et al., 1996). Direct formation of ASD granules by this method reduces additional downstream processing steps, which aids in avoiding potential stability issues during these processes (Dereymaker et al., 2017). In addition, such granules allow an additional coating of suitable excipients which can control the release profiles or enhance the ASD stability (Varum et al., 2011).

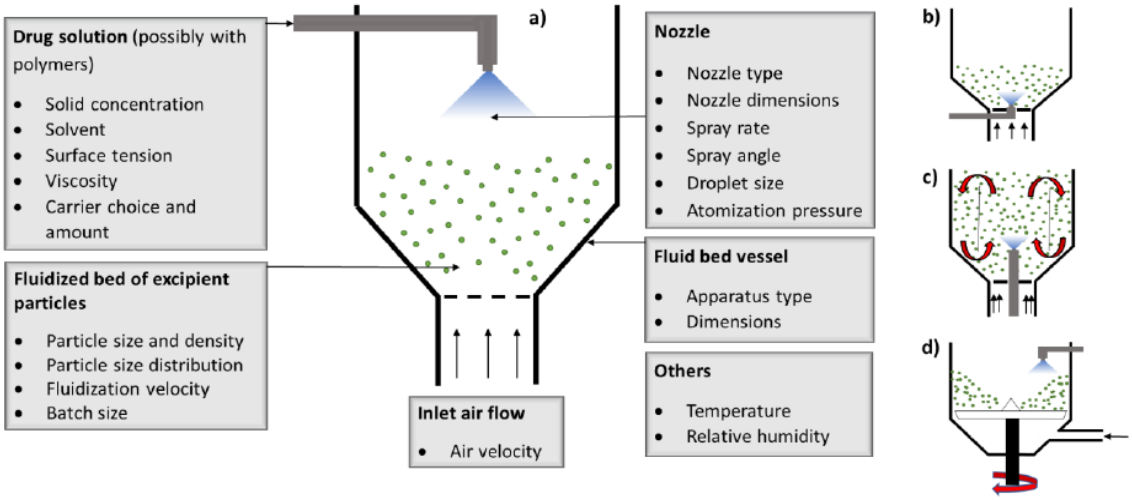


Figure 3: Fluidized bed manufacturing variables affecting product properties and the different types of fluidized bed dryers (a) top spray; (b) bottom spray; (c) Wurster; (d) tangential or side rotor spray.

B. Melting-based methods

In melt-based methods, the formulation components are heated to form dispersions, followed by cooling. Solvent avoidance is a significant benefit of the melting techniques (Repka et al., 2011). However, a major drawback of these methods is that the high temperatures may induce drug degradation. Melting methods also require sufficient solubility/miscibility of drugs in the polymer melt, which can be very difficult for certain molecules to achieve (Huang & Dai, 2014, Patil et al., 2015). An efficient ASD production by melting depends on the operational as well as compositional variables. The use of a polymer in the production of an ASD is of course to stabilize the amorphous form, but it is also important for processing because the polymer provides a molten medium for drug solubilization or dispersion. Therefore, the polymers used in melting processes are usually polymers or waxes with a low melting point or Tg (Crowley et al., 2007). Commonly used carriers include PVP, PVPVA, cellulose esters and acrylates, and polymethacrylate derivatives. There are some commercial polymers specifically designed for melting processes such as HPMCAS, Soluplus®, and Affinisol® HPMC HME (modified HPMC). These carriers can also be used in combination to achieve improved amorphization, stability, dissolution, and bioavailability.

B1. Hot-melt extrusion (HME)

For commercial-scale production, only two types of melting processes are available, hot-melt extrusion (HME) and melt agglomeration. HME, and especially the twin-screw melt extrusion with Meltrex™ as a representative example, is one of the most widely used techniques for producing ASDs (Repka et al., 2011; Patil et al., 2015; Berndl et al., 2011). The drug and the polymer are mixed, melted, dispersed, and then extruded under specific processing conditions (Patil et al., 2015; Berndl et al., 2011). Figure 4 shows the HME process, which can be divided theoretically into five steps, namely: feeding, melting and plasticizing, mixing/kneading and conveying, discharging, and cooling for further downstream processing. Important parts of a hot-melt extruder include a feed hopper, barrel, extrusion screws, torque sensors, heating-cooling system and dies. The HME equipment has a flexible design, which enables processes to be tailored to achieve the desired outcomes and to accommodate varying raw materials, by adjusting the modular design elements, namely the screws and barrels (Breitenbach et al., 2002). It is also possible to apply HME technology to drugs liable to oxidation and hydrolysis by excluding oxygen and moisture from the mixture (Patil et al., 2015; Breitenbach et al., 2002; Wilson M et al., 2012)

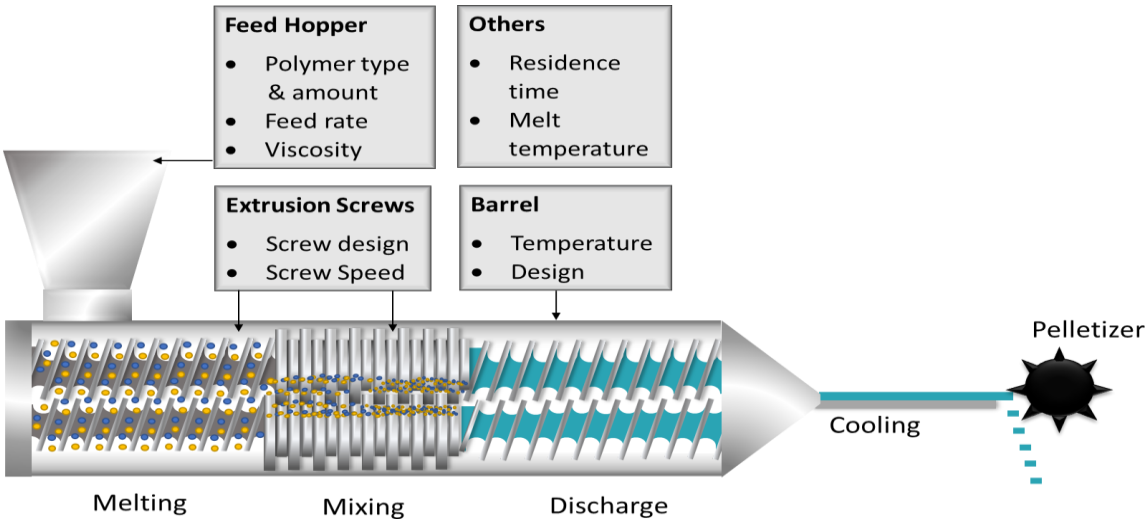


Figure 4: Twin-screw hot-melt extrusion and the associated manufacturing variables impacting product properties.

C. Granulation

Preparation of ASDs by the granulation approach enables the direct generation of ASD granules with a reduced number of manufacturing unit operations and minimized cost for investing in new equipment (Parik 2010; Hirani et al., 2006). Depending on the nature of the binder fluid, granulation can be categorized into solvent evaporation or melting process categories. Several granulation techniques can be utilized to produce ASDs including fluidized bed granulation, tumbling granulation, and mixing granulation (Kwon et al. 2019; Jang et al. 2014; Chen et al., 2014; Shanmugam 2017; Fujimoto et al., 2016; Hansuld & Briens 2014). Figure 5 shows the commonly used high-speed granulator and the associated manufacturing variables affecting ASD properties.

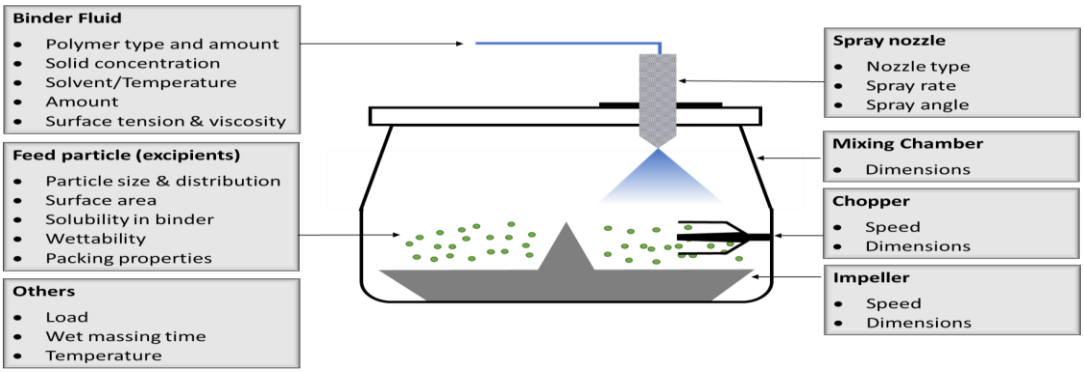


Figure 5 Preparation of ASDs using a high-speed mixer granulator.

The principle of granulation for ASD preparation by solvent evaporation is the same as discussed in the fluidized bed technique section earlier (fluidized bed granulators). In this case, the binder usually consists of a drug dissolved in appropriate solvent(s) which is then added to the remaining excipients of the formulation. There are several examples in the literature which have utilized solvent evaporation-based granulation for the successful preparation of ASDs (Jang et al., 2014; Fujimoto et al., 2016; Trasi et al., 2020, Trasi et al., 2019). In addition, if it is critical to avoid drug exposure to the organic and/or aqueous solvents, the (process of melt agglomeration can be employed wherein a molten mass of the drug and the polymer serves as a binder for forming granules (Shanmugam 2017; Kowalski et al. 2009). This further reduces the drying steps associated with the solvent-based wet granulation process. Melt agglomeration also employs standard granulation equipment such as high shear granulators (Seo 2003; Vilhelmsen et al., 2005) and fluidized bed granulators (Aleksić et al., 2014). The melted drug-polymer mass serves as a binding liquid for granulation, ensuring sufficient homogeneity. Polymers for melt agglomeration

can be liquids such as PEG 300 and caprylocaproyl macrogol-8 glycerides (Labrasol®) or semi-solids like stearoyl polyoxyl- 32 glycerides (Gelucire® 50/13) (Seo 2003; Gupta et al., 2001). Solid polymers with low melting temperature/Tg, such as PEG (3000 and 6000 grades) and poloxamer 188 can also be used. However, similar to other melting processes, the use of high temperatures limits its application to thermally sensitive drugs. The limited choice in carriers is another drawback of this method because high Tg polymers are not suitable. (Vilhelmsen et al., 2005; Passerini et al., 2002)

RESEARCH GAP IDENTIFICATION

- Poorly water-soluble drugs belongs to BCS class II and IV present ongoing challenges with their translation into viable medicinal products.
- The hurdles to their successful oral delivery are a complex web of physical-chemical, biological, physiological and anatomical factors that act independently and in concert to limit drug bioavailability.
- Rate limiting factor is low equilibrium solubility leads to very slow drug dissolution rate and poor intestinal absorption.
- The current formulation strategies to overcome these issues can be separated in two major categories:

a) methods that increase the apparent equilibrium drug solubility and the dissolution rate, and

b) Techniques that increase the dissolution rate and facilitate the formation of metastable supersaturated drug solutions.

OBJECTIVES

a) Pre-formulation Studies and screening of polymers & surfactants.

b) Formulation of solid dispersions via spray congealing and/or other techniques

c) Formula and process optimisation of using above manufacturing techniques

d) In vitro studies, for IVIVC (In vitro in vivo correlation) establishment.

PROPOSED METHODOLOGY

(Methodology can be modified on the basis of resources)

The research aims to formulate a drug product with improved solubility

- Selection of drug candidate (based upon physiochemical characteristics)
- Analytical method development
- Preparation of amorphous solid dispersion using Melt agglomeration and/or Solvent evaporation with amalgamation of adjuvant solubility enhancement techniques (Micronization, pH adjustment etc.) may be investigated
- Experimental study plan as below:
  - ➢ Selection of Polymers and Plasticizers
  - ➢ Miscibility Study of Drug-Polymer & Drug-Polymer-Plasticiser mixture
  - ➢ Feasibility batches with selected polymers and plasticisers
  - ➢ Polymer and plasticiser level optimisation with DoE optimisation designs
  - ➢ Characterization and evaluation of designed experiments
  - a) Solubility measurement in buffers and biorelevant media (pH 1.2, 4.5, 6.8. 7.2, FaSSGF, FeSSGF, FaSSIF, FeSIIF)
  - b) In-vitro dissolution testing in discriminatory media
  - ➢ Stability loading and monitoring of final optimised formulations
  - ➢ *In-vitro* and *in-vivo* correlation establishment.
- Comparison between the different polymers and techniques for solubility enhancement of selected drug candidate and the outcome.

THESIS OUTLINE

Chapter 1: Introduction. It covers the aim and objectives of research topic i.e. quality by design based formulation and characterization of poorly water soluble drug via advanced solubility enhancement techniques

Chapter 2: Literature Review. It cover review of work done on solubility techniques, model drug and solid dispersion.

Chapter 3: Materials and Methods. It covers the list of material, equipments and methods used in research work.

Chapter 4: Result and discussion. It covers the preformulation, characterization and

optimization results of solid dispersion.

Chapter 5: Summary and conclusion. It covers the concise statement and key point of Solubility enhancement.

Chapter 6: References. It coves every source. The reference list entries contain four main component: author, date, title and source.

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CERTIFICATE

(SYNOPSIS APPROVAL CERTIFICATE)

This is to certify that the Synopsis for Ph.D. Thesis titled, "Quality by Design based Formulation and Characterization of Poorly Water Soluble Drug via Advanced Solubility Enhancement Techniques", submitted by **Mr. Ankur Gupta** to the Career Point University, Hamirpur (H.P.), India in partial fulfillment of the requirements for the degree of **DOCTOR OF PHILOSOPHY** in the Division/Department of Pharmaceutical Sciences, **School of Pharmaceutical and Health Sciences** has been approved by the Research Advisory Committee (RAC) after an Oral Examination of the student on dated 12/12/2022

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